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Age of onset in idiopathic (genetic) generalized epilepsies: Clinical and EEG findings in various age groups

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ABSTRACT

Purpose: The prevalence and differences of idiopathic (genetic) generalized epilepsies (IGEs) with atypical age of onset compared to classical IGEs is a matter of debate. We tried to determine the clinical and EEG characteristics of IGEs in various age groups.
Methods: All patients with a clinical diagnosis of IGE were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences from 2008 through 2011. We subdivided the patients into four different age groups: 4 years of age and under, 5–11 years, 12–17 years, and finally, 18 years and above, at the time of their epilepsy onset. Syndromic diagnosis, sex ratio, seizure types and EEG findings were compared. Statistical analyses were performed using Pearson Chi square test.
Results: 2190 patients with epilepsy were registered. 442 patients (20.2%) were diagnosed as having IGEs. Age of seizure onset was 12.4 ± 6.9 years. The peak age of onset had a bimodal appearance. Sixty-seven patients (15.2%) were four years and under at the time of the onset of their disease, 112 persons (25.3%) were 5–11 years, 197 people (44.6%) were 12–17 years of age, and 66 patients (14.9%) had 18 years and above at the onset of their epilepsy. The sex ratio was significantly different between patients in group one compared to groups three and four. All expected seizure types (i.e., generalized tonic–clonic, absence or myoclonic seizures) and all expected EEG abnormalities were observed among all age groups, despite some differences in their prevalence.
Conclusion: Although IGE syndromes are often age dependent and most of them appear within the first two decades of life, adult-onset IGE is not rare. Presentation of IGEs could be different in various age groups, but these differences do not offer pathognomonic or characteristic features at any age.

1. Introduction

Idiopathic (genetic) generalized epilepsies (IGEs) are epilepsy syndromes with generalized seizures, which are probably genetic in nature.[1–3] This encompasses several different syndromes. These syndromes are diagnosed by strict clinical and electroencephalographic features proposed by the International League Against Epilepsy (ILAE).[4] Although IGE syndromes are often age dependent and most of them typically appear within the first two decades of life, there are reports of adult-onset IGE.[5] Early-onset forms of particular syndromes of IGE are also reported in the literature.[6,7] The prevalence, differences and similarities of IGEs with atypical age of onset compared to classical IGEs is a matter of debate in the literature.[5–11] In the current study, we tried to specifically determine the age of onset in patients with IGE to see if there are any specific patterns. We also tried to determine clinical and electrographic characteristics of IGEs in various age groups, with particular attention to the youngest and oldest patients; to see if there are pathognomonic or characteristic features in any particular age group.

2. Materials and methods

In this cross-sectional retrospective chart review study all patients with a clinical diagnosis of idiopathic (genetic) generalized epilepsy were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, which is the only epilepsy clinic in south Iran, from September 2008 through May 2011. The diagnosis of epilepsy was made exclusively by the only epileptologist working at this institution (the first author) and based on clinical grounds and electroencephalographic findings, and all patients had to be under the care of the epileptologist at our institution. Routinely a template with a specific series of questions is being used by the epileptologist to take the history in a standardized manner (Appendix 1) in order to prevent or at least minimize the possibility of missing clinical findings, including

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seizure types. There was no age limit to enter the study. Electroencephalography (EEG) was performed in all patients at the time of referral. Study time for EEG was 10 min and we performed intermittent photic stimulation in all patients. Hyperventilation was typically performed in children above five years of age. The high frequency filter was set to 70 Hz and the low filter was at 0.16 Hz. All the EEGs were assessed by the epileptologist at our institution.

We differentiated the IGE syndromes on the basis of the predominant seizure pattern and the age of onset. We particularly asked about the three major seizure types seen in IGEs in our history taking (i.e., generalized tonic–clonic, absence and myoclonic seizures). Age of onset was considered as the age the patient/caregiver could recall of his/her first seizure of any type (i.e., generalized tonic–clonic, absence or myoclonic seizures). We studied the demographic, clinical and EEG findings in all IGE syndromes, either recognized by ILAE or syndromes under evaluation (see Nordi[4] for definitions and characteristics of IGEs recognized by the ILAE and refer to Panayiotopoulos[12] for syndromes of IGEs not yet recognized by the ILAE).

Age, gender, age at seizure onset, seizure type(s), EEG findings and final syndromic diagnosis of all patients were registered routinely. We arbitrarily subdivided the patients into four different age groups: 4 years of age and under (group one), 5–11 years (group two), 12–17 years (group three), and finally, 18 years and above (group four); based on the age at the time of their epilepsy onset. Then, syndromic diagnosis, sex ratio, seizure types and EEG findings were compared between these age groups. Statistical analyses were performed using Pearson Chi square test to determine potentially significant differences, and a P value less than 0.05 was considered significant. This study was conducted with approval of the Shiraz University of Medical Sciences Review Board.

3. Results

During the study period, 2190 patients with epilepsy were registered at our epilepsy clinic. Four hundred and forty two patients (20.2%) were diagnosed as having IGEs. Of these, 252 patients were female (57%) and 190 (43%) were male. Mean age of seizure onset was 12.4 ± 6.9 years (minimum = 6 month and maximum = 54 years). Fig. 1 shows the distribution of the age of onset in patients with IGE. Sixty-seven patients (15.2%) were four years and under at the time of the onset of their disease, 112 persons (25.3%) were 5–11 years, 197 people (44.6%) were 12–17 years of age, and 66 patients (14.9%) had 18 years and above at the onset of their epilepsy. Table 1 shows the syndromic diagnosis in each age group. Figs. 2–5 show the distribution of the age of onset in four major syndromes of IGE (childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic–clonic seizures only, consecutively). Table 2 shows the sex distribution in each age group. The sex ratio was significantly different between patients in group one compared to the patients in groups three ($P = 0.03$) and four ($P = 0.02$). This ratio was not significantly different in two by two comparisons of other age groups. Table 3 shows the frequency of various seizure types in each age group. All the expected seizure types (i.e., generalized tonic–clonic, absence and myoclonic seizures) were observed in all age groups, despite some differences, some of which were statistically significant. Table 4 shows the various EEG abnormalities in each age group. In some age groups, particular EEG abnormalities were more frequently observed compared to the others, but all the expected EEG abnormalities [polyspikes, 3-Hz generalized spike-wave (GSW) complexes and 3.5–6 Hz GSW complexes, alone or in combinations] were observed in all four age groups. Photoparoxysmal response was observed in none of the patients in group 1, in 12 patients (10.7%) in group 2, in 8 (4.1%) in group 3, and in 6 (9.1%) in group 4. The differences between patients in group 1 and others were significant. The rate of photoparoxysmal responses were not significantly different in two by two comparisons of the other age groups with one exception; it was significantly more frequent in group 2 compared to group 3 ($P = 0.02$).

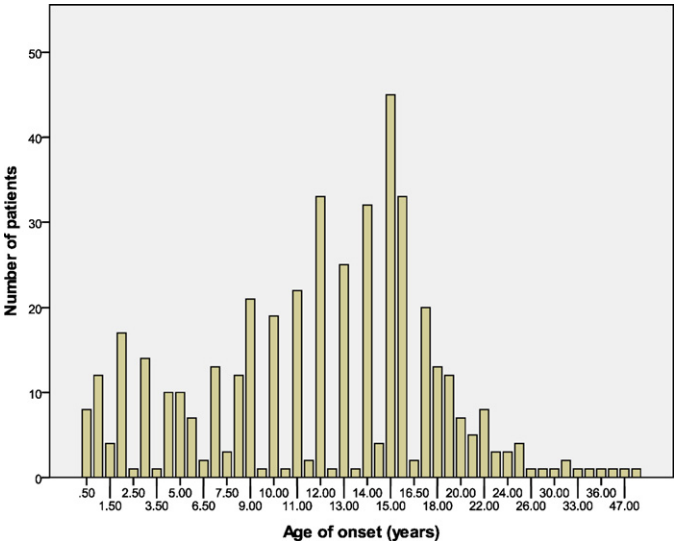

Fig. 1. Age of seizure onset was 12.4 ± 6.9 years (minimum = 6 month and maximum = 54 years). Sixty-seven patients (15.2%) were four years and under at the time of the onset of their disease, 112 persons (25.3%) were 5–11 years, 197 people (44.6%) were 12–17 years of age, and 66 patients (14.9%) had 18 years and above at the onset of their epilepsy. The peak age of onset has a bimodal appearance with a small peak at 2 years and a large peak at 15 years of age.

Table 1
Syndromic diagnosis in patients with IGE in different age groups.

Age group	Syndromic diagnosis	Frequency	Percent
0–4 years at onset (group 1)	*EGTCS only*	*36*	*53.7*
N = 67	CAE	16	23.9
	BMEI	6	9
	Myoclonic-astatic	3	4.5
	EMA	1	1.5
	Jeavons syndrome	1	1.5
	Unidentified	4	6
5–11 years at onset (group 2)	*CAE*	*33*	*29.5*
N = 112	JAE	29	25.9
	JME	24	21.4
	EGTCS only	21	18.8
	Jeavons syndrome	3	2.7
	Unidentified	2	1.8
12–17 years at onset (group 3)	*JME*	*133*	*67.5*
N = 197	JAE	36	18.3
	EGTCS only	26	13.2
	Jeavons syndrome	2	1
18 years and above at onset (group 4)	*JME*	*43*	*65.2*
	EGTCS only	11	16.7
N = 66	Phantom absences	8	12.1
	JAE	2	3.0
	Unidentified	2	3.0

Syndromes of IGE include: benign myoclonic epilepsy in infancy (BMEI), epilepsy with myoclonic absences (EMA), epilepsy with myoclonic-astatic seizures, childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), epilepsy with generalized tonic–clonic seizures (EGTCS) only, perioral myoclonia with absences (PMA), idiopathic generalized epilepsy with phantom absences, and Jeavons syndrome (eyelid myoclonia with absences).

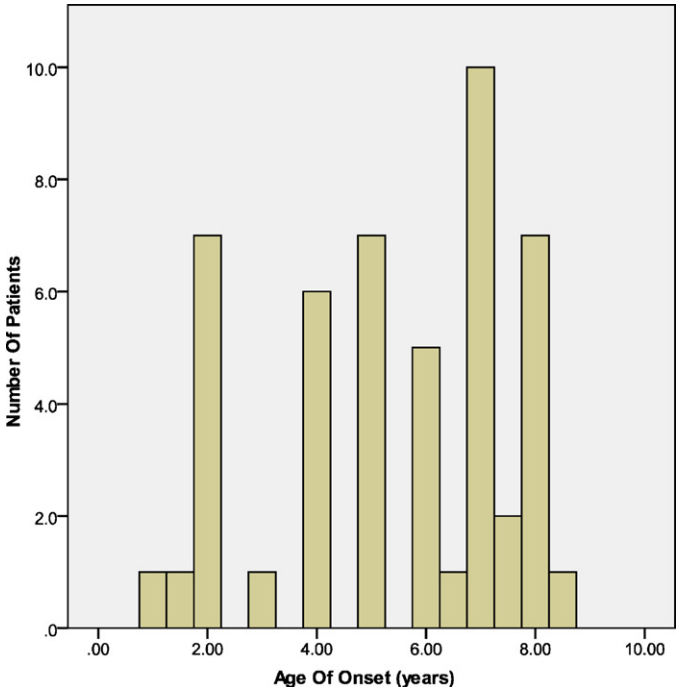

Fig. 2. In patients with CAE, age of seizure onset was 5 ± 2 years (minimum = 1 and maximum = 8.5 years). The peak age of onset was at 7 years of age.

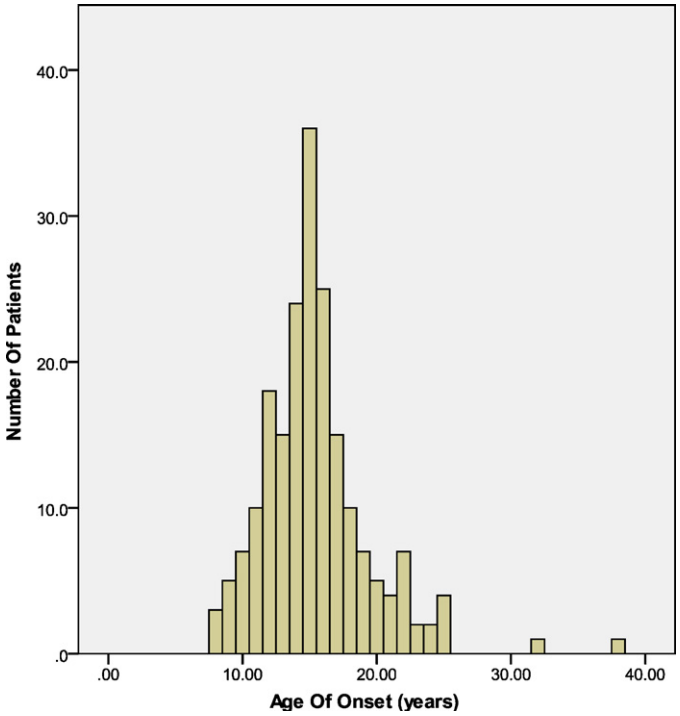

Fig. 4. In patients with JME, age of seizure onset was 15 ± 4 years (minimum = 8 and maximum = 38 years). The peak age of onset was at 15 years of age.

4. Discussion

Idiopathic (genetic) generalized epilepsies (IGEs) are common epilepsy syndromes. The general frequency of IGEs was 20% in our study, which is concordant with many previous studies.[13] The peak age of onset of IGEs had a bimodal appearance with a small peak at 2 years and a large peak at 15 years of age (Fig. 1), in our study. It sharply declined after 17 years of age; however, the frequency of adult-onset IGE was 15% in our study. This frequency was reported to be 8.5%[11] to 28%[10] in previous studies. The observed differences could be methodological (e.g., differences in definitions applied and cut off ages used) or biological (e.g., genetic variations among different populations). Further studies with particular attention to these observed discrepancies are required. Unfortunately, it is

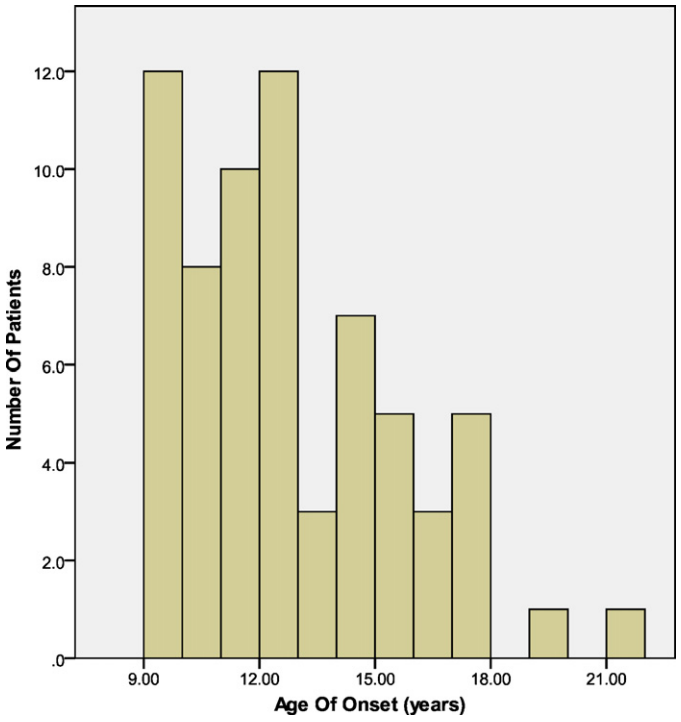

Fig. 3. In patients with JAE, age of seizure onset was 12 ± 3 years (minimum = 9 and maximum = 21 years).

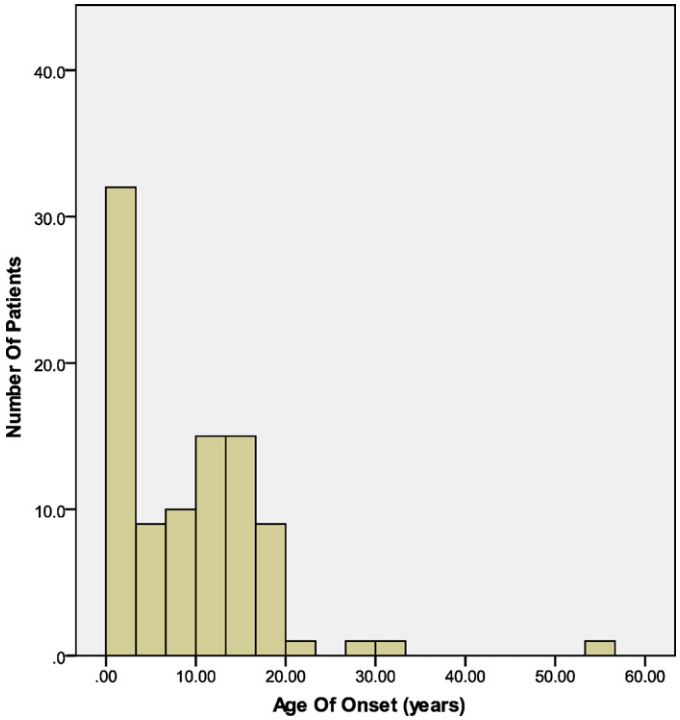

Fig. 5. In patients with EGTCS only, age of seizure onset was 9 ± 8 years (minimum = 6 months and maximum = 54 years).

Table 2
Sex distribution in patients with IGE in different age groups.

Age group	Gender	Frequency	Percent
Group 1 (*N* = 67)	*Male*	37	55.2
	Female	30	44.8
Group 2 (*N* = 112)	Male	49	43.7
	Female	63	56.3
Group 3 (*N* = 197)	Male	80	40.6
	Female	117	59.4
Group 4 (*N* = 66)	Male	24	36.4
	Female	42	63.6

often taught that adults with new-onset epilepsy should be assumed to have localization-related (focal) epilepsy. Staring spells are loosely labeled as complex partial seizures, and generalized tonic–clonic seizures are assumed to be secondarily generalized. This assumption is inappropriate and should be avoided.[14] One should consider that a significant proportion of IGEs begins beyond adolescence.

The most common syndrome in patients with adult-onset IGE was juvenile myoclonic epilepsy (JME), followed, with a large gap, by epilepsy with generalized tonic–clonic seizures only (EGTCS only) and phantom absences, in our study. In two previous studies,[10,11] EGTCS only was the most common diagnosis in adults with IGE, followed by myoclonic seizures and absences, consecutively. Again, the observed differences could be methodological or biological. A correct diagnosis of epilepsy syndromes needs a standardized approach, particularly with regards to taking a detailed history. The routine use of a standard proforma (as in this study) minimizes the risk of missing clinical findings, including seizure types, and most of the time leads to a correct diagnosis. In a previous study, only 32% of patients with JME were correctly diagnosed at referral. The main factors responsible for misdiagnosis were failure to elicit a history of myoclonic jerks and misinterpretation of myoclonic jerks.[15] Indeed, a considerable delay of approximately five years has been observed in the diagnosis of JME when and where private physicians were possibly not familiar with this syndrome, in another study.[16]

The sex ratio has been investigated in patients with IGE in previous studies. In our study, a male preponderance was observed in patients in group one (four years of age and under at the onset), while in other groups women outnumbered men. This female preponderance became more obvious at higher ages. The sex ratio (female to male) was 0.8 in group 1, 1.3 in group 2, 1.5 in group 3, and 1.8 in group 4. In Cutting's study, women outnumbered men in patients with adult-onset IGE (sex ratio = 1.2).[8] However, in Marini's and Nicolson's studies men outnumbered women in patients with adult-onset IGE.[10,11] In Chaix's study, girls outnumbered boys in early-onset absence epilepsy.[9] These discrepancies could be biological (e.g., genetic variations among different populations); however, they need further investigation. Our finding that a female preponderance became more obvious at higher ages, needs more exploration in future studies. Maybe sex hormones play an important role, or maybe females are more susceptible for some other reasons. This merits consideration in future investigations.

Table 3
Frequency of various seizure types in patients with IGE in different age groups.[a]

	Number of patients with GTCS		Number of patients with myoclonic seizure		Number of patients with absence seizure	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Group 1 (*N* = 67)	46	68.7	14	20.9	19	28.4
Group 2 (*N* = 112)	89	79.5	51	45.5	71	**63.4**
Group 3 (*N* = 197)	176	89.3	143	**72.6**	88	44.7
Group 4 (*N* = 66)	64	**97.0**	44	66.7	33	50.0

[a] Some patients had multiple seizure types.

Table 4
EEG abnormalities in patients with IGE in different age groups.

Age group	EEG finding	Frequency	Percent
Group 1 (*N* = 66)	3 Hz GSW	20	30.3
	3.5–6 Hz GSW	17	25.8
	3 Hz GSW + Polyspikes	11	16.7
	3.5–6 Hz GSW + Polyspikes	9	13.6
	Normal	4	6
	Others (e.g., focal slow waves, generalized slow waves, etc.)	4	6
	Polyspikes	1	1.5
Group 2 (*N* = 111)	3.5–6 Hz GSW + Polyspikes	31	27.9
	3 Hz GSW + Polyspikes	24	21.6
	3 Hz GSW	20	18
	3.5–6 Hz GSW	14	12.6
	Normal	11	9.9
	Polyspikes	7	6.3
	Others	4	3.6
Group 3 (*N* = 193)	3.5–6 Hz GSW + Polyspikes	53	27.5
	3 Hz GSW + Polyspikes	36	18.7
	Normal	31	16.1
	3.5–6 Hz GSW	29	15
	3 Hz GSW	26	13.5
	Polyspikes	14	7.2
	Others	4	2
Group 4 (*N* = 64)	3.5–6 Hz GSW + Polyspikes	13	20.3
	3 Hz GSW	12	18.8
	3.5–6 Hz GSW	11	17.2
	Normal	11	17.2
	3 Hz GSW + Polyspikes	10	15.6
	Polyspikes	3	4.7
	Others	4	6.2

In eight patients EEG was not available. GSW: generalized spike-waves.

It is well-known that the presentation of IGEs could be different in various age groups. In our study, GTCS and myoclonic seizures were more frequent in older patients, while absence seizure was more frequent in preschool and school age children. However, despite these clinical differences, there was no pathognomonic or even characteristic feature for any particular age group and all expected seizure types (GTCS, myoclonic and absences) could be seen in patients with IGE in all age groups.

The EEG is a valuable ancillary test in making the diagnosis of IGE. The presence of generalized spike-wave complexes and/or polyspikes adds to the probability of a correct diagnosis as IGE and supports this diagnosis.[17] The prevalence of specific EEG abnormalities were occasionally different in various age groups in our study, however all expected EEG abnormalities (polyspikes, 3-Hz GSW complexes and 3.5–6 Hz GSW complexes, alone or in combinations) were observed in all age groups. In a previous study, no differences of EEG features were found between the classic adolescent-onset and the adult-onset IGEs.[5] Similar results were obtained in our study (Table 5). This finding has basic pathophysiological significance and supports the hypothesis that IGE syndromes in different age groups share common biologic (probably genetic) determinants.[5] Clinical expression depends on more than the EEG and the nature of the cortical discharges alone does not determine the seizure type or course!

Table 5
EEG abnormalities in adolescent-onset compared to adult-onset IGEs.

EEG abnormality	Group 3 ($N=193$)	Group 4 ($N=64$)	P value
3.5–6 Hz GSW + Polyspikes	53	13	0.25
3 Hz GSW + Polyspikes	36	10	0.58
3.5–6 Hz GSW	29	11	0.67
3 Hz GSW	26	12	0.3
Polyspikes	14	3	0.47
Normal	31	11	0.83
Others	4	4	–

5. Limitations of the study

1. This was a clinic-based series and may not represent the full spectrum of IGEs, because the mildest disease varieties may not be referred to a university clinic. Selection bias always remains probable in this kind of study.
2. Age limits and even differences in clinical manifestations of some syndromes are not fully clear yet. For example, differentiation of JME from JAE is not always easy. We tried to differentiate these syndromes on the basis of predominance of seizure pattern, but in practice, some syndromes of IGE have overlapping symptoms and are sometimes difficult to distinguish. In this study, we could not ascertain the syndromic classification in eight patients (Table 1).
3. Since most syndromes of IGEs are defined in part by age, finding that certain syndromes are clustered by age is to some extent tautological. However, the finding that, the most common syndrome in patients with adult-onset IGE was JME merits consideration, particularly at the time of history taking.
4. Some seizure types might appear earlier than others in patients with IGE. Therefore, the age at which one sees the patient might influence what type of seizures and syndrome he/she has. In practice, sometimes following people for longer periods might change the diagnosis.

6. Conclusion

IGE encompasses several different syndromes, which are diagnosed by strict clinical features. We recommend using a template (Appendix 1) with a specific series of questions to take the history in a standardized manner in all patients. Although IGE syndromes are often age dependent and most of them appear within the first two decades of life, adult-onset IGE is not rare. The peak age of onset of IGEs has a bimodal appearance with a small peak at 2 years and a large peak at 15 years of age. Presentation of IGEs (either clinical or electrographic) could be different in various age groups, but these differences do not offer pathognomonic or characteristic features at any age. In other words, similarities are more than differences between various age groups with regards to the clinical and electrographic features of IGEs. This finding supports the hypothesis that IGE syndromes in different age groups share common biologic determinants.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest statement

Michael Sperling: consulting and speaking for UCB Pharma. Other authors have no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2012.04.004.

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